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Regioselective Deiodination of Thyroxine by Iodothyronine Deiodinase Mimics: An Unusual Mechanistic Pathway Involving Cooperative Chalcogen and Halogen Bonding

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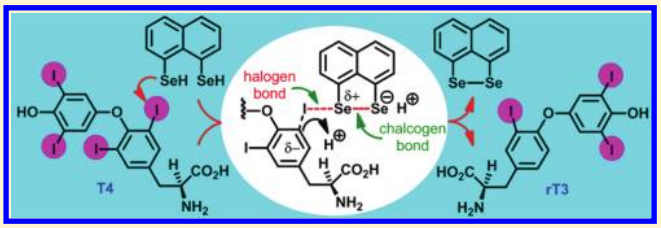
Supporting Information

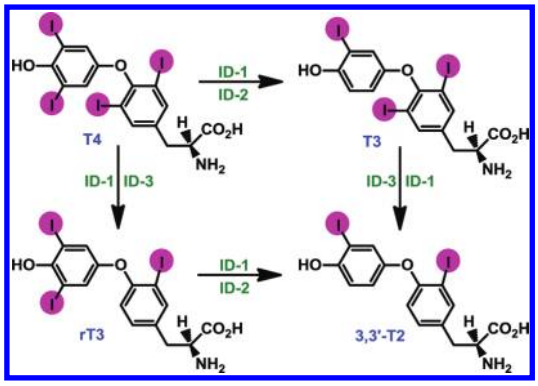
ABSTRACT: Iodothyronine deiodinases (IDs) are mammalian selenoenzymes that catalyze the conversion of thyroxine (T4) to 3,5,3′-triiodothyronine (T3) and 3,3′,5′-triiodothyronine (rT3) by the outer- and inner-ring deiodination pathways, respectively. These enzymes also catalyze further deiodination of T3 and rT3 to produce a variety of di- and monoiodo derivatives. In this paper, the deiodinase activity of a series of *peri*-substituted naphthalenes having different amino groups is described. These compounds remove iodine selectively from the inner-ring of T4 and T3 to produce rT3 and 3,3′-diiodothyronine (3,3′-T2), respectively. The naphthyl-based compounds having two selenols in the *peri*-positions exhibit much higher deiodinase activity than those having two thiols or a thiol−selenol pair. Mechanistic investigations reveal that the formation of a halogen bond between the iodine and chalcogen (S or Se) and the *peri*-interaction between two chalcogen atoms (chalcogen bond) are important for the deiodination reactions. Although the formation of a halogen bond leads to elongation of the C−I bond, the chalcogen bond facilitates the transfer of more electron density to the C−I σ^* orbitals, leading to a complete cleavage of the C−I bond. The higher activity of amino-substituted selenium compounds can be ascribed to the deprotonation of thiol/selenol moiety by the amino group, which not only increases the strength of halogen bond but also facilitates the chalcogen−chalcogen interactions.



INTRODUCTION

Iodothyronine deiodinases (IDs) are mammalian selenoenzymes that are involved in the activation and inactivation of thyroid hormones.[1] Type-1 and -2 deiodinases (ID-1 and ID-2) catalyze the outer-ring (5′) deiodination of thyroxine (3,5,3′,5′-tetraiodothyronine, T4) to produce 3,5,3′-triiodothyronine (T3). These two enzymes also convert 3,3′,5′-triiodothyronine (reverse T3 or rT3) to 3,3′-diiodothyronine (3,3′-T2) by 5′-deiodination (Scheme 1).[2] The type-3 deiodinase (ID-3), on the other hand, catalyzes the conversion of T4 to rT3 by an inner-ring (5) deiodination.[2,3] It is known that ID-3 plays a crucial role in the maintenance of serum T3 concentration by converting T3 to 3,3′-T2, which is believed to be a key step in the protection of tissues from excess thyroid hormone.[2−4] Although deiodinases are essential for the function of thyroid gland, the mechanism of the deiodination reactions remains unknown.

Scheme 1. Activation and Inactivation of Thyroid Hormones by Three Iodothyronine Deiodinases (ID-1, ID-2, and ID-3)



The interesting regioselective deiodinations of thyroid hormones by different deiodinases have sparked interest in the development of simple selenium compounds as mimics of these redox enzymes.[5,6] Goto et al. reported a synthetic selenol that converts *N*-butyrylthyroxine methyl ester to the corresponding triiodo derivative by 5′-deiodination.[6] We have shown that compound **1**, having two thiol moieties, and compound **2**, having a thiol−selenol pair in the *peri*-positions, convert T4 and T3 to rT3 and 3,3′-T2, respectively, by 5-deiodination.[7] Very recently, we reported, in a preliminary communication, that compound **3**, bearing two selenol moieties, is more active than **1** and **2** in the deiodination of T4 under physiologically relevant conditions.[8] However, the mechanism by which these compounds remove iodine selectively from the 5-position of T4 or T3 is not clear. Herein we report the synthesis, deiodinase activity, and mechanism of action of a series of *peri*-

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substituted naphthalene derivatives. We also show for the first time that the *peri*-interactions between two chalcogen atoms (chalcogen bond) facilitate the halogen-bond-assisted activation of the carbon−iodine bond in T4 and related compounds.

EXPERIMENTAL SECTION

General Procedure. *n*-Butyllithium (*n*-BuLi) was purchased from Acros Chemical Co. (Belgium). Selenium powder, DTT, T4, rT3, and T3 were obtained from Aldrich Chemical Co. Liquid state NMR spectra were recorded in $CDCl_3$ or d_4-MeOH as a solvent. ^1H (400 MHz), ^{13}C (100.56 MHz), and ^{77}Se (76.29 MHz) NMR spectra were obtained using a Bruker 400 MHz NMR spectrometer. Chemical shifts are cited with respect to $SiMe_4$ as internal (^1H and ^{13}C) and Me_2Se as external (^{77}Se) standard. Thin-layer chromatography analyses were carried out on precoated silica gel plates (Merck), and spots were visualized by UV irradiation. Column chromatography was performed on glass columns loaded with silica gel or on an automated flash chromatography system (Biotage) by using preloaded silica cartridges. High-performance liquid chromatography (HPLC) experiments were carried out on a Waters Alliance System (Milford, MA) consisting of a 2695 separation module and a 2996 photodiode-array detector. The assays were performed in 1.8 mL sample vials, and a built-in autosampler was used for sample injection. The HPLC system was controlled with EMPOWER software (Waters Corporation, Milford, MA).

Deiodination Assay. The deiodination reactions were carried out in 100 mM phosphate buffer (pH 7.5) with 10 mM dithiothreitol (DTT) at 37 °C. Selenols and thiols were freshly prepared by reducing the corresponding selenenyl sulfides, diselenides, or disulfides with $NaBH_4$ prior to use. The reaction products were analyzed by reverse-phase HPLC (Lichrospher C18 column, 4.6 μm, 150 mm × 5 mm) with gradient elution using acetonitrile/ammonium acetate (pH 4.0) as the mobile phase. The formation of rT3 was monitored at λ= 275 nm, and the amounts of deiodinated products formed in the reactions were calculated by comparing the peak areas.

Synthesis of ***4****.* Compound **4** was synthesized by following a literature procedure.[9c] ^1H NMR ($CDCl_3$) δ (ppm): 7.15 (d, J = 8 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.35 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 116.4, 122.1, 128.4, 135.2, 136.2, 144.5; ESI-MS (m/z) calcd for $C_{10}H_6S_2$ [M]+: 189.99, found 189.87.

Synthesis of ***5****.* Compound **5** was synthesized by following a literature procedure.[9d] ^1H NMR ($CDCl_3$) δ (ppm): 7.18 (d, J = 7.2 Hz, 1H), 7.23−7.31 (m, 3H), 7.34 (d, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 118.8, 119.8, 122.7, 123.8, 128.0, 128.3, 136.6, 137.2, 141.1, 145.1; ^{77}Se NMR ($CDCl_3$) δ (ppm): 556; ESI-MS (m/z) calcd for $C_{10}H_6SSe$ $[M]^+$: 237.93, found 237.80.

Synthesis of ***6****.* Compound **6** was synthesized by following a literature procedure.[9c] ^1H NMR ($CDCl_3$) δ (ppm): 7.23 (d, J = 7.6 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.47 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 121.5, 124.2, 128.1, 137.9, 138.3, 141.2; ^{77}Se NMR ($CDCl_3$) δ (ppm): 415. ESI-MS (m/z) calcd for $C_{10}H_6Se_2$ $[M]^+$: 285.88, found 285.56.

Synthesis of ***24****.* This compound was synthesized by Vilsmeier−Haack formylation by following a procedure reported for the corresponding disulfide, naphthalene-1,8-disulfide-2-carboxaldehyde.[7,10] The 2-formyl naphthalene selenenyl sulfide was synthesized by adding $POCl_3$ (0.9 g, 0.6 mL, 12.9 mmol) dropwise to a stirred solution of selenenyl sulfide **5** (0.8 g, 3.4 mmol) in dry DMF (10 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature, and the stirring was continued for 24 h under nitrogen. To this, water was added to give a yellow solid, which was extracted with EtOAc (200 mL) and washed three times with brine. The organic layer was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The desired compound **24** was purified from the other isomers by silica gel column chromatography using toluene as mobile phase. ^1H NMR ($CDCl_3$) δ (ppm): 7.45 (d, J = 6.8 Hz, 1H), 7.56 (1H, J = 7.6 Hz, 1H), 7.59−7.64 (m, 2H), 7.77 (d, J = 8.4 Hz, 1H), 10.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 120.5, 121.3, 124.6, 128.8, 129.1, 130.8, 137.7, 138.3, 149.4, 154.9, 187.5; ^{77}Se NMR ($CDCl_3$) δ (ppm): 773; ESI-MS (m/z) calcd for $C_{11}H_6OSSe$ $[M]^+$ 265.93, found 265.92.

Synthesis of ***25****.* This compound was synthesized by following the procedure given for compound **24** and purified from the other isomers by silica gel column chromatography using toluene as mobile phase. ^1H NMR ($CDCl_3$) δ (ppm): 7.47 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 7.61−7.69 (m, 2H), 7.72 (d, J = 7.2 Hz, 1H), 10.18 (s,1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 122.8, 123.4, 125.1, 129.5, 130.4, 130.8, 139.5, 146.8, 155.2, 188.6; ^{77}Se NMR ($CDCl_3$) δ (ppm): 408, 673; ESI-MS (m/z) calcd for $C_{11}H_6OSe_2$ $[M]^+$: 313.87, found 313.91.

Synthesis of ***26****.* To a solution of naphthalene-1,8-disulfide-2-carboxaldehyde (500 mg, 2.29 mmol) in 30 mL of dry acetonitrile was added dropwise a 30% solution of methyl amine (1.8 g, 50.84 mmol). It was stirred at 60 °C for 8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure. The resulting Schiff base was purified by column chromatography using petroleum ether/ethyl acetate as eluent to give **26** as a red solid in 87% yield: ^1H NMR ($CDCl_3$) δ (ppm): 3.75 (s, 3H), 7.39−7.44 (m, 2H), 7.45−7.47 (m, 1H), 7.49 (s, 2H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 43.8, 118.3, 120.4, 122.8, 125.9, 127.2, 128.7, 135.5, 135.7, 147.5, 148.9, 157.4; ESI-MS (m/z) calcd for $C_{12}H_9NS_2$ $[M]^+$: 231.02, found 230.84.

Synthesis of ***27****.* To a solution of naphthalene-1,8-selenenylsulfide-2-carboxaldehyde (300 mg, 1.13 mmol) in 20 mL of dry acetonitrile was added dropwise a 30% solution of methyl amine (0.7 g, 22.62 mmol). The resulting reaction mixture was stirred at 60 °C for 14 h. The progress of the reaction was monitored by TLC. After completion of the reactions, the solvent was evaporated under reduced pressure. The resulting Schiff base was purified by column chromatography using petroleum ether/ethyl acetate as eluent to give **27** as a brown solid in 78% yield: ^1H NMR ($CDCl_3$) δ (ppm): 3.83 (s, 3H), 7.46−7.48 (m, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.70−7.72 (m, 1H); ^{77}Se NMR ($CDCl_3$) δ (ppm): 770.

Synthesis of ***28****.* To a solution of naphthalene-1,8-selenenylsulfide-2-carboxaldehyde (300 mg, 1.13 mmol) in 20 mL of dry acetonitrile was added dropwise a 70% solution of ethyl amine (1.01 g, 22.62 mmol). The resulting reaction mixture was stirred at 60 °C for 14 h. The progress of the reaction was monitored by TLC. The solvent was evaporated under reduced pressure. The resulting Schiff base was purified by column chromatography using petroleum ether/ethyl acetate as eluent to give **28** as a brown solid in 72% yield: ^1H NMR ($CDCl_3$) δ (ppm): 1.51 (t, J = 7.2 Hz, 3H), 4.03 (q, J = 6.4 Hz, 2H), 7.42−7.46 (m, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.52, (d, J = 8.4 Hz, 1H), 7.68−7.70 (m, 1H), 8.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 18.3, 50.1, 120.1, 122.3, 125.0, 126.2, 127.8, 128.5, 135.8, 150.1, 150.7, 154.6; ^{77}Se NMR ($CDCl_3$) δ (ppm): 762.

Synthesis of ***29****.* To a solution of naphthalene-1,8-diselenide-2-carboxaldehyde (300 mg, 0.96 mmol) in 20 mL dry acetonitrile was added dropwise a 30% solution of methyl amine (595 mg, 19.2 mmol). The resulting reaction mixture was stirred at 60 °C for 12 h. The progress of the reaction was monitored by TLC. The solvent was evaporated under reduced pressure. The resulting Schiff base was purified by column chromatography using petroleum ether/ethyl acetate as eluent to give **29** as a red solid in 82% yield: ^1H NMR ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 7.39 (t, J = 7.6 Hz, 1H), 7.56−7.59 (m, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.85−7.87 (m, 1H), 8.8 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 42.0, 122.0, 125.3, 125.5, 126.9, 128.2, 129.4, 137.1, 138.4, 146.1, 151.6, 158.0; ^{77}Se NMR ($CDCl_3$): 339, 696; ESI-MS (m/z) calcd for $C_{12}H_9NSe_2$ $[M + H]^+$: 327.91, found 327.92.

Synthesis of ***30****.* To a solution of naphthalene-1,8-diselenide-2-carboxaldehyde (300 mg, 0.96 mmol) in 20 mL of dry acetonitrile was added dropwise a 70% solution of ethyl amine (865 mg, 19.2 mmol). The resulting reaction mixture was stirred at 60 °C for 12 h. The progress of the reaction was monitored by TLC. The solvent was evaporated using reduced pressure. The resulting Schiff base was purified by column chromatography using petroleum ether/ethyl acetate as eluent to give **30** as a red solid in 85% yield: ^1H NMR ($CDCl_3$) δ (ppm): 1.56 (t, J = 6.8 Hz, 3H), 4.05 (q, J = 7.2 Hz, 2H), 7.38 (t, J = 8 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H), 7.72 (d, J = 8.4, 1H),

7.84 (d, J = 7.2 Hz, 1H), 8.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 18.1, 50.6, 122.0, 125.4, 125.5, 127.0, 128.2, 129.4, 138.4, 146.1, 146.1, 151.4, 155.9; ^{77}Se NMR ($CDCl_3$) δ (ppm): 340, 690; ESI-MS (m/z) calcd for $C_{13}H_{11}NSe_2$ $[M + H]^+$: 341.93, found 341.94.

Synthesis of ***31***. To a solution of naphthalene-1,8-diselenide-2-carboxaldehyde (300 mg, 0.96 mmol) in 20 mL of dry acetonitrile was added dropwise *n*-propyl amine (1.13 g, 19.2 mmol). The resulting reaction mixture was stirred at 60 °C for 12 h. The progress of the reaction was monitored by TLC. The solvent was evaporated under reduced pressure. The resulting Schiff base was purified by column chromatography using petroleum ether/ethyl acetate as eluent to give **31** as a red solid in 92% yield: ^{1}H NMR ($CDCl_3$) δ (ppm): 1.06 (t, J = 7.4 Hz, 3H), 1.95 (m, 2H), 3.96 (t, J = 7.4 Hz, 2H), 7.39 (t, J = 7.7 Hz, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 8 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 8.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 12.45, 25.9, 58.2, 122.0, 125.3, 125.5, 127.0, 128.2, 129.3, 137.0, 138.4, 146.1, 151.4, 156.4; ^{77}Se NMR ($CDCl_3$) δ (ppm): 341, 690; ESI-MS (m/z) calcd for $C_{14}H_{13}NS_2$ $[M + H]^+$: 355.94, found 355.73.

Synthesis of ***32***. To a solution of naphthalene-1,8-diselenide-2-carboxaldehyde (300 mg, 0.96 mmol) in 20 mL of dry acetonitrile was added dropwise isopropyl amine (1.13 g, 19.2 mmol). The resulting reaction mixture was stirred at 60 °C for 12 h. The progress of the reaction was monitored by TLC. The solvent was evaporated under reduced pressure. The resulting Schiff base was purified by column chromatography using petroleum ether/ethyl acetate as eluent to give **32** as a red solid in 90% yield: ^{1}H NMR ($CDCl_3$) δ (ppm): 1.53 (d, J = 6.4 Hz, 6H), 4.05−4.10 (m, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 8.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 26.1, 58.0, 122.1, 125.3, 125.4, 127.2, 128.2, 129.4, 136.9, 138.4, 146.0, 150.9, 154.2; ^{77}Se NMR ($CDCl_3$) δ (ppm): 341, 678; ESI-MS (m/z) calcd for $C_{14}H_{13}NS_2$ $[M + H]^+$: 355.94, found 355.76.

Synthesis of ***33***. Compound **26** (150 mg, 0.65 mmol) was dissolved in 30 mL of MeOH−$CHCl_3$ (5:1). $NaBH_4$ (737 mg, 19.5 mmol) was added to the above solution. The color of the solution turned to pale yellow immediately. The reaction mixture was stirred at room temperature for 2 h. The resulting yellow solution was poured into 100 mL of water and extracted with dichloromethane. The dichloromethane extract was then dried and evaporated to give a yellow solid, which was then purified by column chromatography using petroleum ether−ethyl acetate as eluent to give **33** as a yellow solid in 78% yield: ^{1}H NMR ($CDCl_3$) δ (ppm): 2.43 (s, 3H), 3.89 (s, 2H), 7.12−7.18 (m, 2H), 7.21−7.26 (m, 1H), 7.30−7.33 (2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 36.0, 54.6, 111.7, 121.3, 122.4, 127.7, 128.0, 130.1, 135.3, 136.5, 142.7, 144.7; ESI-MS (m/z) calcd for ESI calcd for $C_{12}H_{11}NS_2$ $[M]^+$: 233.04, found 233.82.

Synthesis of ***34***. Compound **27** (100 mg, 0.38 mmol) was dissolved in 20 mL of MeOH−$CHCl_3$ (5:1). $NaBH_4$ (408 mg, 10.8 mmol) was added to the above solution. The color of the solution turned to pale yellow immediately. The reaction mixture was stirred at room temperature for 4 h. The resulting yellow solution was poured into 100 mL of water and extracted with 20 mL of dichloromethane. The dichloromethane extract was then dried and evaporated to give a yellow solid, which was then purified by column chromatography using petroleum ether/ethyl acetate as eluent to give **34** as a brown solid in 68% yield: ^{1}H NMR ($CDCl_3$) δ (ppm): 2.53 (s, 3H), 3.91 (s,3H), 7.06 (d, J = 8 Hz, 1H), 7.17−7.21 (m, 1H), 7.27−7.29 (m, 2H), 7.44 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 36.7, 54.5, 120.0, 121.2, 124.4, 126.6, 127.6, 131.5, 136.0, 139.5, 146.2; ^{77}Se NMR ($CDCl_3$) δ (ppm): 577; ESI-MS (m/z) calcd for $C_{12}H_{11}NSSe$ $[M]^+$: 280.98, found 280.92.

Synthesis of ***35***. Compound **28** (100 mg, 0.34 mmol) was dissolved in 20 mL of MeOH−$CHCl_3$ (5:1). $NaBH_4$ (388 mg, 10.26 mmol) was added to the above solution. The reaction mixture was stirred at room temperature for 4 h. The resulting yellow color solution was poured into 100 mL of water and extracted with 20 mL of dichloromethane. The dichloromethane extract was then dried and evaporated to give a yellow solid, which was then purified by column chromatography using petroleum ether−ethyl acetate as eluent to give **35** as a brown solid in 65% yield: ^{1}H NMR ($CDCl_3$) δ (ppm): 1.23 (t, J = 7.2 Hz, 3H), 2.73−2.78 (q, J = 7.2 Hz, 2H), 3.94 (s, 1H), 7.04 (d, J = 8 Hz, 1H), 7.17−7.21 (m, 1H), 7.26−7.29 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.2, 44.9, 52.5, 120.0, 121.2, 124.4, 126.5, 127.6 132.1, 136.0, 137.8, 139.5, 146.2; ^{77}Se NMR ($CDCl_3$) δ (ppm): 562; ESI-MS (m/z) calcd for $C_{13}H_{13}NSSe$ $[M + H]^+$: 296.00, found 295.80.

Synthesis of ***36***. Compound **29** (200 mg, 0.62 mmol) was dissolved in 30 mL of MeOH−$CHCl_3$ (5:1). $NaBH_4$ (468 mg, 12.4 mmol) was added to the above solution. The red solution turned to pale yellow immediately. The reaction mixture was stirred at room temperature for 3 h. The resulting red solution was poured into 100 mL of water and extracted with 40 mL of dichloromethane. The dichloromethane extract was then dried and evaporated to give a yellow solid, which was then purified by column chromatography using petroleum ether/ethyl acetate as eluent to give **36** as a red solid in 78% yield: ^{1}H NMR ($CDCl_3$) δ (ppm): 2.51 (s, 3H), 3.95 (s, 2H), 7.06 (d, J = 8 Hz, 1H), 7.16−7.20 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.46−7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ (ppm): 36.3, 55.5, 123.0, 123.5, 124.9, 127.0, 127.6, 133.6, 136.8, 139.6, 140.7, 141.8. ^{77}Se NMR ($CDCl_3$) δ (ppm): 342, 480; ESI-MS (m/z) calcd for $C_{12}H_{11}NSe_2$ $[M]^+$: 327.14, found 327.66.

Synthesis of ***37***. Compound **30** (200 mg, 0.59 mmol) was dissolved in 30 mL of MeOH−$CHCl_3$ (5:1). $NaBH_4$ (446 mg, 11.8 mmol) was added to the above solution. The red solution turned to pale yellow immediately. The reaction mixture was stirred at room temperature for 3 h. The resulting red solution was poured into 100 mL of water and extracted with 40 mL of dichloromethane. The dichloromethane extract was then dried and evaporated to give a red solid, which was then purified by column chromatography using petroleum ether−ethyl acetate as eluent to give **37** as a red solid in 82% yield: ^{1}H NMR ($CDCl_3$) δ (ppm): 2.21−2.23 (t, J = 6.8 Hz, 3H), 2.68−2.73 (q, J = 6.8 Hz, 2H), 3.94 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.17 (t, J = 8 Hz, 1H), 7.38 (d, J = 8 Hz, 1H), 7.47 (t, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.2, 44.5, 53.5, 123.0, 123.5, 124.8, 126.6, 127.6, 134.2, 136.8, 139.6, 140.6, 141.7; ^{77}Se NMR ($CDCl_3$) δ (ppm): 345, 466; ESI-MS (m/z) calcd for $C_{13}H_{13}NSe_2$ $[M + H]^+$ = 343.93, found 343.67.

Synthesis of ***38***. Compound **31** (180 mg, 0.51 mmol) was dissolved in 30 mL of MeOH−$CHCl_3$ (5:1). $NaBH_4$ (385 mg, 10.20 mmol) was added to the above solution. The red solution turned to pale yellow immediately. The reaction mixture was stirred at room temperature for 3 h. The resulting red color solution was poured into 100 mL of water and extracted with 40 mL of dichloromethane. The dichloromethane extract was then dried and evaporated to give a red solid, which was then purified by column chromatography using petroleum ether−ethyl acetate as eluent to give **38** as a red solid in 85% yield: ^{1}H NMR ($CDCl_3$) δ (ppm): 0.94 (t, J = 8 Hz, 3H), 1.64−1.70 (m, 2H), 2.68 (t, J = 7.2 Hz, 2H), 3.95 (s, 2H), 7.08 (d, J = 8 Hz, 1H), 7.17 (t, J = 8 Hz, 1H), 7.38−7.44 (m, 2H), 7.48 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 12.1, 22.7, 51.5, 53.4, 123.1, 123.4, 124.9, 127.1, 127.6, 133.0, 136.9, 139.4, 141.2, 141.7; ^{77}Se NMR ($CDCl_3$) δ (ppm): 345, 470; ESI-MS (m/z) calcd for $C_{14}H_{15}NSe_2$ $[M]^+$: 355.95, found 356.97.

Synthesis of ***39***. Compound **32** (220 mg, 0.62 mmol) was dissolved in 30 mL of MeOH−$CHCl_3$ (5:1). $NaBH_4$ (471 mg, 12.45 mmol) was added to the above solution. The red solution turned to pale yellow immediately. The reaction mixture was stirred at room temperature for 3 h. The resulting red solution was poured into 100 mL of water and extracted with 40 mL of dichloromethane. The dichloromethane extract was then dried and evaporated to give a red solid, which was then purified by column chromatography using petroleum ether−ethyl acetate as eluent to give **39** as a dark red solid in 85% yield: ^{1}H NMR ($CDCl_3$) δ (ppm): 1.22 (s, 6H), 2.95−3.01 (m, 1H), 3.97 (s, 2H), 7.04 (d, J = 8 Hz, 1H), 7.17 (t, J = 8 Hz, 1H), 7.39 (d, J = 8 Hz, 1H), 7.44−7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 22.8, 49.7, 51.2, 123, 123.5, 124.8, 126.7, 127.6, 134.6, 136.8, 139.6, 141.1, 141.7; ^{77}Se NMR ($CDCl_3$) δ (ppm): 350, 445; ESI-MS (m/z) calcd for $C_{14}H_{15}NSe_2$ $[M]^+$: 356.95, found 356.98.

Single Crystal X-ray Crystallography. X-ray crystallographic studies were carried out on a Bruker CCD diffractometer with graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å)

controlled by a Pentium-based PC running the SMART software package.[11] Single crystals were mounted at room temperature on the ends of glass fibers, and data were collected at room temperature. The structures were solved by direct methods and refined using the SHELXTL software package.[12] All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were assigned idealized locations. Empirical absorption corrections were applied to all structures using SADABS.[13,14] The structures were solved by direct methods (SIR-92) and refined by full-matrix least-squares procedures on $F2$ for all reflections (SHELXL-97).

Crystal Data for ***30****.* $C_{13}H_{11}NSe_2$; M_r = 339.15, orthorhombic $P\bar{1}$, a = 7.6025(8) Å, b = 15.0667(17) Å, c = 10.5922(10) Å, α = 90°, β = 90°, γ = 90°, V = 1213.3(2) Å^3, Z = 4, Mo Kα radiation (λ = 0.71073 Å), T = 293(2) K, $R1$ = 0.0400, $wR2$ = 0.1018 ($I > 2\sigma(I)$), $R1$ = 0.0507, $wR2$ = 0.1114 (all data).

Crystal Data for ***31****.* $C_{14}H_{13}NSe_2$, M_r = 353.17, monoclinic $P\bar{1}$, a = 10.8085(11) Å, b = 11.5763(11) Å, c = 10.5415(10) Å, α = 90°, β = 93.079(4)°, γ = 90°, V = 1317.1(2) Å^3, Z = 4, Mo Kα radiation (λ = 0.71073 Å), T = 293(2) K, $R1$ = 0.0406, $wR2$ = 0.1124 ($I > 2\sigma(I)$), $R1$ = 0.0818, $wR2$ = 0.1395 (all data).

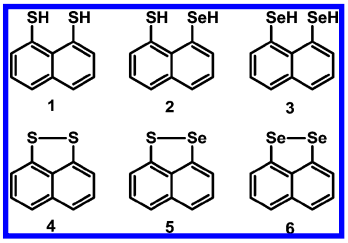
Crystal Data for ***35****.* $C_{13}H_{13}NSSe$; M_r = 294.3, triclinic $P1$, a = 7.9434(7) Å, b = 8.0334(8) Å, c = 19.9028(2) Å, α = 80.665(6)°, β = 80.049(6)°; γ = 82.737(7)°, V = 1228.0(2) Å^3, Z = 4, Mo Kα radiation (λ = 0.71073 Å), T = 293(2) K, $R1$ = 0.0655, $wR2$ = 0.1275 ($I > 2\sigma(I)$); $R1$ = 0.2531, $wR2$ = 0.1917 (all data).

Crystal Data for ***37****.* $C_{13}H_{13}NSe_2$; M_r = 341.17, triclinic $P\bar{1}$, a = 9.0033(15) Å, b = 10.0187(14) Å, c = 14.8110(19) Å, α = 74.780(8)°, β = 82.647(9)°, γ = 89.847(9)°, V = 1277.8(3)Å^3, Z = 4, Mo Kα radiation (λ = 0.71073 Å), T = 293(2) K, $R1$ = 0.0558, $wR2$ = 0.1564 ($I > 2\sigma(I)$); $R1$ = 0.0558, $wR2$ = 0.1564 (all data).

Computational Methods. All calculations were performed using the Gaussian03 and Gaussian09 suites of quantum chemical programs.[15] The hybrid Becke 3−Lee−Yang−Parr (B3LYP) exchange correlation functional was employed to predict the minimum energy molecular geometries of the compounds.[16] Geometries were fully optimized in the gas phase at the B3LYP level of theory by using the 6-31+G* basis set for all atoms except iodine, for which it does not exist. Therefore, the 6-311G** basis set was used for iodine. Frequency calculations were performed on each optimized structure using the same basis set to ensure that it was a minimum on the potential energy surface. NBO calculations[17] were performed with the 6-311G** basis set for iodine and 6-311+G** for all other atoms and the same level of theory. Electrostatic potential maps of thyroid hormones were mapped on the surface of molecular electron density 0.01 au by using Gauss View 5.0 software.

RESULTS AND DISCUSSION

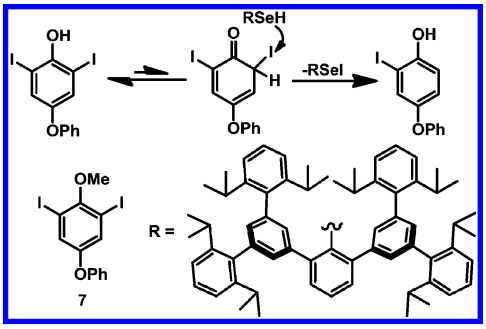
The deiodination of T4 and T3 by compounds **1**−**3** in the presence of dithiothreitol (DTT) was studied by using a HPLC method.[7,8] Compounds **1**−**3** were obtained by reducing the corresponding dichalcogenides **4**−**6** with $NaBH_4$ in phosphate buffer. The amounts of rT3 and 3,3′-T2 formed in these reactions were calculated from the respective peak areas. Interestingly, compounds **1**−**3** remove iodine exclusively from the 5-position of T4 to produce rT3 as the only deiodinated product. However, these compounds do not mediate the 5′-deiodination, as no 3,3′-T2 formation was observed when pure rT3 was treated with **1**, **2**, or **3**. In contrast, treatment of T3 with compounds **1**−**3** produced 3,3′-T2, indicating that compounds **1**−**3** mediate 5-deiodination of both T4 and T3. A comparison of the deiodinase activities indicated that compound **3**, having two selenol moieties, is almost 75-fold more active than compound **1**. On the other hand, only a 13-fold enhancement in the activity was observed when one of the thiols in compound **1** was replaced by a selenol (compound **2**). The importance of the selenocysteine (Sec) residue in the catalytic center of ID-3 has been demonstrated previously by Kuiper et al.[18] They showed that the substitution of Sec by a cysteine (Cys) significantly reduces the catalytic efficiency and that the substrate turnover numbers for the deiodinations of T4 and T3 by the Cys mutant were 6- and 2-fold lower, respectively, than for the wild-type enzyme.



The deiodination of T4 by compounds **1**−**3** occurred even in the absence of DTT. When T4 was treated with an excess amount of compound **2** or **3** (5 equiv), complete conversion of T4 into rT3 was observed. Analysis of the reaction products by HPLC and mass spectrometry indicated that compounds **1**, **2**, and **3** were oxidized to the dichalcogenides **4**, **5**, and **6**, respectively. As the formation of **4**−**6** was observed even under nitrogen atmosphere, the second thiol/selenol group may act as a cofactor not only for the deiodination reaction but also for the release of iodide (I^-) from the intermediates. Therefore, the rate of deiodination depends on the nature of the groups present in the 1,8-positions. It has been proposed that the release of iodide from iodothyronines occurs during the first half of the ID-1 cycle[19] and that one of the Cys residues in the active site of ID-1 may interact with the selenium center to generate an intramolecular selenenyl sulfide (-Se−S-) bond.[20] These observations suggest that the thiol cofactor (DTT) may interact with the enzyme to regenerate the active site only after the release of iodide.

It has been proposed previously that the 5′-deiodination of thyroxine by ID-1 or synthetic selenol (RSeH) may involve nucleophilic attack of the selenol (or selenolate) on the iodine center of the keto form (Scheme 2). In this case, the

Scheme 2. Proposed Mechanism for the 5′-Deiodination by Enol−Keto Tautomerism[6]

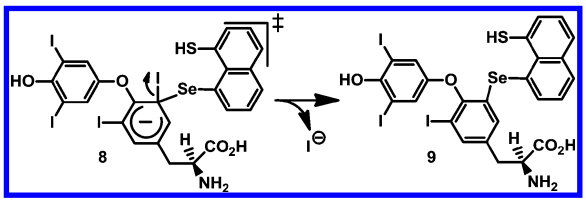


deiodination is accompanied by the formation of a selenenyl iodide (RSeI) species. In agreement with this mechanism, compound **7**, which cannot undergo tautomerization to the keto form, did not undergo deiodination upon treatment with RSeH (Scheme 2).[6] ID-2, which mediates the 5′-deiodination exclusively, may also follow a similar mechanism, although the formation of a selenenyl iodide intermediate has not been proposed. Kuiper et al.[21] proposed a mechanism for the 5′-deiodination of T4 by ID-2 in which the nucleophilic Sec residue attacks at the 2′-position of T4 to form an intermediate

having a carbon−selenium covalent bond. The abstraction of iodonium ion (I^+) by thiol cofactor leads to the formation of an ID-2−T3 complex and a cofactor sulfenyl iodide. While the rapid disproportionation of the sulfenyl iodide produces iodide (I^-) and disulfide, a thiol attack at the enzyme intermediate regenerates the enzyme active site with the elimination of T3. However, it is not clear whether ID-3 uses any additional functional groups for the selective removal of iodine from the inner ring of T4 (5-deiodination). It should be noted that ID-1, which mediates the conversion of T4 to T3, is also capable of removing iodine from T3 to produce 3,3′-T2 by 5-deiodination. As all three enzymes contain Sec in their active sites and share many common features in their amino acid sequences, they are expected to follow a similar mechanism for the 5- and 5′-deiodinations.

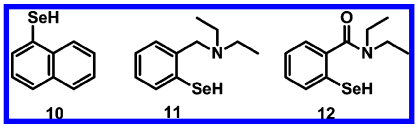
It is known that aryl halides in which the halogen substituent is *ortho* or *para* to an electron-withdrawing group are activated for nucleophilic aromatic substitutions *via* the addition/elimination mechanism (S_NAr).[22] For example, the reactions of *o*- and *p*-nitroaryl iodides with thiolates have been shown to follow such a mechanism.[22,23] Tiecco et al. reported that alkylselenium groups can be introduced into an aromatic ring by nucleophilic displacement of unactivated halogen atoms.[24] The reaction of compound **2** with T4 in the absence of DTT produces the selenenyl sulfide **5** and rT3. This reaction can follow the S_NAr mechanism, in which the selenium substituted compound **9** and iodide can be generated through formation a Meisenheimer complex (**8**) (Scheme 3). The free thiol group

Scheme 3. Possible Mechanism for the Deiodination of T4 by Compound 2



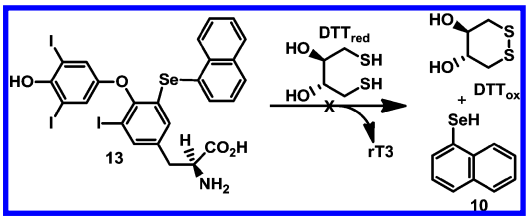
present in the 8-position can then attack at the electrophilic selenium center to produce the selenenyl sulfide **5** with the elimination of rT3. This mechanism, in principle, may account for the initial rapid release of iodide from T4 in the absence of DTT. However, we could not detect the formation of any substituted products. The formation of rT3 and **5** was observed even at −20 °C, indicating that the reaction does not produce any stable intermediates.

To understand whether a rapid nucleophilic attack of thiol at the selenium center is responsible for the facile formation of rT3, we have studied the reactions of T4 with compounds **10**−**12**, which do not have any additional thiol or selenol



moieties. The ^{77}Se NMR chemical shift observed for compound **10** (−34 ppm) indicates that the selenol moiety in this compound is highly nucleophilic. Therefore, the reaction of T4 with **10** is expected to produce the substituted compound **13** *via* the S_NAr mechanism. However, no such compound was detected by ^{77}Se NMR spectroscopy or mass spectral analysis, indicating that the deiodination of T4 by compound **3** may not follow the S_NAr mechanism shown in Scheme 3. Furthermore, the formation of rT3 was not observed even after the addition of DTT (Scheme 4). Similarly, no deiodination was observed

Scheme 4. Attempted Deiodination of T4 by Compound 10 in the Presence of Dithiothreitol (DTT)



when compound **11**, which has a *tert*-amino group capable of deprotonating the selenol moiety, or compound **12**, which contains an amide group in the close proximity of selenium, was employed. A large upfield shift in the ^{77}Se NMR signal for compound **11** (54 ppm) relative to that of PhSeH (145 ppm) suggests that the selenol moiety in **11** is more nucleophilic than that in PhSeH. These observations indicate that the presence of an additional thiol or selenol group in proximity to the selenium atom is more important for the 5-deiodination than basic amino groups.

The mechanism of deiodination of T4 by compounds **1**−**3** may involve the formation of a halogen bond[25] between a thiol/selenol group and an iodine atom. Halogen bonds play key roles in the recognition of thyroid hormones. It has been shown that T4 forms short I···O interactions with its transport protein transthyretin and that T4 can bind to RNA sequences through halogen bonds.[26] Recently, Bayse and Rafferty studied S···I and Se···I interactions in model compounds by using density functional theory (DFT) calculations to understand the mechanism of thyroid hormone deiodination.[27] On the basis of detailed theoretical investigations, they proposed that the halogen bonding between selenium and iodine may play an important role in the deiodination. The activation barriers for deiodination of an aromatic iodide by MeSeH and MeSH were calculated to be 17.6 and 19.8 kcal·mol^{-1}, respectively, indicating that the substitution of selenol by thiol marginally increases the activation barrier. It has also been shown that deprotonation of the selenol moiety in MeSeH significantly strengthens the halogen bond and shortens the Se···I distance.[27] To understand the nature of iodine atoms present in thyroid hormones, we have carried out DFT calculations of T4, T3, rT3, and 3,3′-T2 at the B3LYP/6-311G** (for iodine) and 6-31+G* (for other atoms) levels.[15] The electrostatic potential maps obtained from these calculations indicate that the iodine atoms have significant positive potential regions (σ-hole)[28] for possible halogen bonding with sulfur or selenium (Figure 1). The role of σ-hole in halogen bonding has been studied extensively for small molecules.[29]

When the selenolate form of compound **10** (Figure 2a) interacts with iodobenzene (Figure 2b, a model compound), a halogen bonded adduct (Figure 2c, **15**) is formed. The charges on the selenium and iodine atoms in **15** indicate that the formation of a halogen bond between the selenolate and iodine leads to a considerable decrease in the electron density around the selenium atom and an increase in the electron density around the iodine atom. A further decrease in the negative charge on selenium was observed when the strength of the halogen bond was increased by introducing fluorine atoms in

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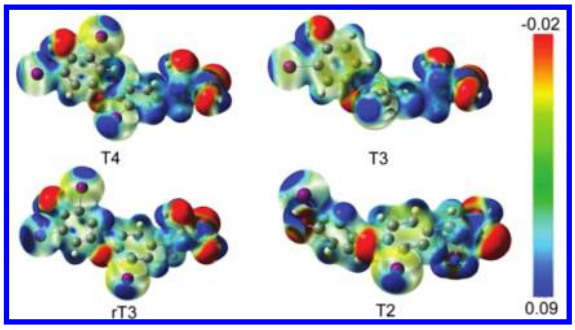

Figure 1. Electrostatic potential maps of thyroid hormones, showing regions of positive potential (σ-hole) on iodine atoms.

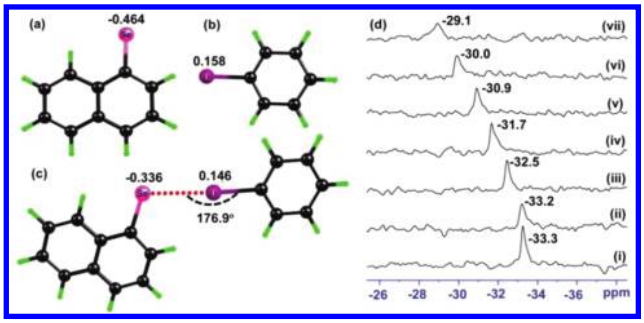

Figure 2. (a) Charges obtained from natural bond orbital (NBO) analysis for the selenolate form of compound **10**, (b), iodobenzene, and (c) halogen-bonded adduct **15**. (d) A downfield shift in the ^{77}Se NMR spectra of compound **10** upon addition of iodobenzene (0 (i), 5 (ii), 10 (iii), 20 (iv), 30 (v), 50 (vi), 70 (vii) equiv), indicating the formation of complex **15**.

the phenyl ring (Figure S46 of the Supporting Information). As previously observed for a variety of halogen bonded compounds,[30] the Se···I−C angle in **15** is almost 180°, indicating the donation of a Se lone pair to the σ^* orbital of the C−I bond. The formation of a σ-hole on selenium was clearly observed for the model selenenyl iodide (Figure S46 of the Supporting Information).[31] In agreement with the theoretical data, addition of iodobenzene to compound **10** led to a significant downfield shift in the ^{77}Se NMR spectrum (Figure 2d), indicating the formation of the halogen bonded adduct (**15**). An increase in the strength of the halogen bond was observed when 1-iodo-4-nitrobenzene was used instead of iodobenzene (Figure S41 of the Supporting Information). A marginal decrease in the electron density upon interaction with iodine is sufficient for the selenium atom to accept electrons from donor groups to form a chalcogen bond.[32] Therefore, the introduction of a thiolate/selenolate at the 8-position in compound **10** is expected to favor the formation of chalcogen bonds through *peri*-interactions.[33] As the thiolate/selenolate at the 1,8-positions can form a covalent bond upon oxidation of one of these substituents, the interaction between two chalcogen atoms leads to the formation of a covalent bond with a release of iodide.

As can be seen from Figure 3 and Table 1, the strength of the halogen bond depends not only on the chalcogen atom that interacts with iodine but also on the second chalcogen that is involved in the *peri*-interactions. A comparison of the halogen bonding energies obtained for different S···I and Se···I complexes (**14**−**17**) indicates that the replacement of a thiolate in complex **14** by a selenolate moiety (complex **15**) leads to only a marginal increase (~1.7 kcal·mol^{-1}) in the halogen bond

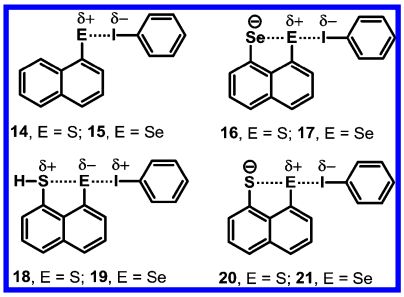

Figure 3. Halogen bonding between thiolate/selenolate and iodine. The $\delta+$ and $\delta-$ signs in the structures do not represent the actual positive or negative charges; instead, they are intended to indicate the decrease and increase in the electron density, respectively, relative to that of free thiolate/selenolate and iodine atom before forming halogen bonding.

Table 1. Halogen Bonding Energy and Bond Order Calculated for Different Thiolate/Selenolate−Iodobenzene Adducts[a]

		bond order		
compd	$E_{S/Se}$···I (kcal·mol^{-1})	S/Se···E	E···I	C−I
14	21.73		0.208	0.855
15	23.43		0.236	0.835
16	52.90	0.048	0.400	0.625
17	68.00	0.083	0.454	0.522
18	5.04[b]	0.101	0.180	0.877
19	20.71[b]	0.077	0.197	0.860
20	55.72	0.047	0.419	0.610
21	74.32	0.079	0.473	0.511

[a]The structures were optimized at the DFT level by using B3LYP/6-311G** for iodine and 6-31+G* for other atoms. The NBO and Wiberg bond order analyses were performed with the 6-311G** basis set for iodine and 6-311+G** for all other atoms and at the same level of theory. [b]The decrease in S/Se···I interaction energy is due to the movement of electron density from thiolate/selenolate to the undissociated thiol.

energy. On the other hand, the halogen bonding interaction in complexes **16** and **17** having a thiolate−selenolate pair and two selenolates, respectively, is much stronger than that of **14** and **15**, which lack the additional selenolate group. Furthermore, the stronger halogen bonding in complex **17** as compared to that of **16** is due to the formation of a chalcogen bond between the two selenium atoms. As a result, the Se−Se bond order in **17** was found to be much higher than the Se−S bond order in **16**. Similarly, a significant decrease in the C−I bond order was observed for **17** as compared to that for **16** (Table 1). Therefore, simple selenols such as PhSeH and **10**, which lack any additional thiol or selenol groups, do not exhibit deiodinase activity, as the strength of halogen bond is not sufficient to cleave the C−I bond. Furthermore, the formation of a stable selenenyl iodide does not appear to be a driving force for the deiodination reaction, as compounds **11** and **12**, capable of forming stable selenenyl iodides,[34] do not remove iodine from T4 or T3.

A comparison of the halogen bonding interactions in complexes **18**−**21** shows some interesting features. Complexes **18** and **19**, having the thiol in its protonated form, exhibit weak halogen bonding. The halogen bond energies for **18** (5.04 kcal·mol^{-1}) and **19** (20.71 kcal·mol^{-1}) were found to be lower than those of **14** (21.73 kcal·mol^{-1}) and **15** (23.43 kcal·mol^{-1}), respectively, indicating that the introduction of a thiol group in

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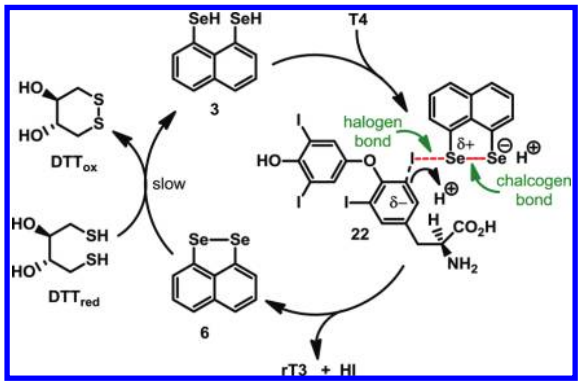
compounds **14** and **15** decreases the strength of halogen bonds. This is probably due to the donation of electrons by the thiolate/selenolate to the sulfur atom of the protonated thiol. Interestingly, when a thiolate instead of thiol was employed for the calculations, a dramatic increase in the strength of the halogen bond was observed. The halogen bond energies for **20** (55.72 kcal·mol^{-1}) and **21** (74.32 kcal·mol^{-1}) were found to be remarkably higher than those of **18** and **19**, respectively. The energy for compound **21**, having a thiolate−selenolate pair, is significantly higher than that of compound **17**, which contains two selenolate moieties in the 1,8-positions.[35] Therefore, the differences in the deiodinase activity between different naphthyl-based compounds can be ascribed to various degrees of ionization of the thiol and selenol moieties. While the selenol group in compound **3** is predominantly in its anion selenolate form at physiological pH, the thiol moieties in compounds **1** and **2** are expected to be only partly ionized. Interestingly, the deiodinase activity of compound **2** was found to be similar to that of **3** at pH 11.0 (Figure S47 of the Supporting Information), which is in agreement with the theoretical observations.

On the basis of the experimental observations and theoretical data, a mechanism for the deiodination of T4 by compound **3** can be proposed (Scheme 5). According to this mechanism, the initial interaction of one of the selenol (selenolate) moieties with an iodine atom leads to the formation of a halogen bond. The transfer of electron density from selenium to the σ^* orbital of the C−I bond generates a σ-hole or partial positive charge on the selenium atom, which facilitates an interaction between the halogen-bonded selenium atom and the free selenol (selenolate) moiety (intermediate **22**). The selenium−selenium interaction (chalcogen bond) strengthens the halogen bond, leading to a heterolytic cleavage of the C−I bond. The protonation of the resulting carbanion leads to the formation of rT3. On the other hand, the formation of an Se−Se bond produces the diselenide **6** with elimination of iodide as HI. The reductive cleavage of the Se−Se bond in compound **6** regenerates the diselenol **3**. However, the reduction of compound **6** by DTT is not a favored process, as the Se−Se bond in this compound is conformationally restricted. It should be noted that the endogenous cofactor used by the deiodinases for the deiodination of T4 and T3 is not known, and therefore, DTT has been used extensively for *in vitro* experiments.[1−3]

Scheme 5. Proposed Mechanism for the Deiodination of Thyroxine (T4) by Compound 3 Involving Chalcogen and Halogen Bonding



The formation of chalcogen- and halogen-bonded adducts (Scheme 5) also explains why a dramatic increase in the deiodinase activity is observed when both the thiol groups in compound **1** are replaced by selenols, but only a marginal increase in the activity is observed when one of the thiol groups in **1** is replaced by a selenol. It should be noted that the selenol (selenolate) moiety abstracts iodine from T4 or T3 as iodonium ion (I^+) and eliminates as iodide (I^-). Although the electrons required for such conversion are provided by one of the selenol (selenolate) moieties, the donation of electrons is facilitated by the *peri*-interactions. Although thiolate is a better donor than selenolate for the formation of a chalcogen bond and selenolate is a slightly better donor than thiolate for the formation of a halogen bond (Table 1), the deprotonation of both the selenols in compound **3** is probably responsible for its higher activity as compared to that of **2** at physiological pH.[35] Furthermore, the selenium center in the halogen-bonded adducts **17** and **21** is more electrophilic than the sulfur center in compounds **16** and **20**, which may account for the higher activity of compounds **2** and **3** as compared to that of **1**.[36]

Although the phenolic ring (5′) deiodination of T4 can take place by a mechanism similar to the one shown in Scheme 5, the reason for the selectivity of compounds **1**−**3** toward the tyrosyl ring (5) deiodination is not clear. As the chemical reactivity of the phenolic ring iodines is expected to be somewhat different from that of the tyrosyl ring iodines, the compounds that can form stronger halogen bonds with iodines may mediate both 5- and 5′-deiodinations. Similarly, such compounds may mediate further deiodination of rT3 and 3,3′-T2 to produce 3′,5′-T2 and 3′-T1 by tyrosyl ring deiodination under appropriate conditions. It should be noted that both ID-1 and ID-3 are capable of converting rT3 to 3′,5′-T2 by tyrosyl ring deiodination. However, such reactions may require longer reaction time and, therefore, are believed to lie off the main catalytic pathway. In compounds **1**−**3**, the rigidity of the naphthalene backbone does not allow a closer approach of the two chalcogen atoms, which may disfavor the formation of stronger halogen bonds with iodothyronines.[37] Our preliminary studies show that the strength of the halogen bond decreases upon removal of one of the iodines from the tyrosyl ring. Therefore, T4 may form stronger halogen bonded adducts with compounds **1**−**3** as compared to rT3.

In the deiodination of T4 and T3 catalyzed by ID-3, the thiol group of the conserved Cys residue (Figure 4) may interact with selenium to activate the C−I bond. Sun et al. have proposed that the active site Cys in ID-1 may play an important role in reducing the oxidized selenium species (possibly selenenyl iodide) to form an intramolecular selenenyl sulfide bond.[20] A further reduction by DTT then regenerates the selenol. However, it is not clear whether the conserved Cys residue in ID-3 forms a selenenyl sulfide with Sec upon deiodination. The mechanism shown in Scheme 5 and the requirement of high DTT concentrations for an effective deiodination suggest that the ID-3-mediated deiodination may

Human	:	RPLVLNFGSCTUPPF
Rat	:	RPLVLNFGSCTUPPF
Chicken	:	RPLILNFGSCTUPPF
Xenopus	:	RPLVVNFGSCTUPPF
Rana	:	RPLVLNFGSCTUPPF
Tilapia	:	RPLILNFGSCSUPPF
Consensus	**:**	**RPLVLNFGSCTUPPF**

Figure 4. Amino-acid sequences at the active sites of ID-3 from different species indicating the conserved Cys (C) and Sec (U) residues.

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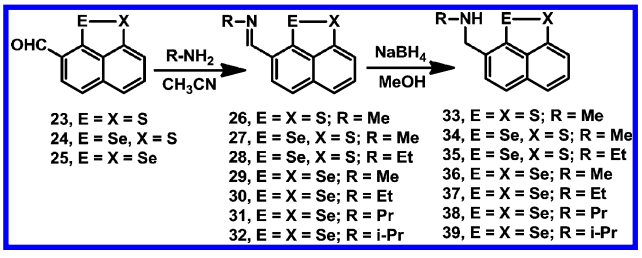
involve the formation a selenenyl sulfide intermediate, which is reduced by DTT. This is in agreement with the observation that the release of iodide from T4 can occur even in the absence of DTT. However, this depends on the redox states of Sec and Cys residues in the native protein. When these two residues form an intramolecular selenenyl sulfide linkage upon auto-oxidation before the deiodination experiments, strong reducing agents such as DTT are required to activate the enzyme.

In addition to Sec and Cys residues, one or more histidines (His) at the active sites of deiodinases appear to play an important role in the deiodination reaction. Köhrle and others have proposed that one of the His residues at the active site of ID-1 may activate the Sec residue toward nucleophilic attack by forming a selenolate–imidazolium zwitterion.[38] The important role of the His residue in the ID-1-mediated deiodination has been proposed on the basis of experiments with histidine-directed reagents, pH-dependent kinetic properties, and site-directed mutagenesis studies.[2b,38] In agreement with this, Goto et al.[6] reported that the 5′-deiodination of *N*-butyrylthyroxine methyl ester by an organoselenol (Scheme 2) takes place only in the presence of triethylamine. They have proposed that the efficiency of the deiodination process largely depends on the nucleophilicity of the selenol functionality. It should be noted that the His residues corresponding to positions 158 and 174 in human ID-1 are conserved in ID-2 and ID-3.[2a] However, the formation of a selenolate–imidazolium ion pair has not been proposed yet for the ID-3 enzyme. However, the inactivity of compound **11** bearing a reactive selenolate moiety indicates that additional interactions at the active site of ID-3 may be required for the deiodination.

To understand the role of basic amino groups in the deiodination reactions, we have synthesized compounds **33**–**39** starting from the dichalcogenides **4**–**6**. The formylation of compounds **4**–**6** by $POCl_3$/DMF (Vilsmeier–Haack reaction)[9,10] afforded the corresponding aldehydes (**23**–**25**), which upon reaction with primary amines produced the Schiff bases **26**–**32**. The ^{77}Se NMR spectra of **27**–**32** (678–770 ppm) show strong noncovalent Se··· N interactions. Single crystal X-ray studies of some of these dichalcogenides (**30**, **31**, **35**, **37**) also indicate the formation of chalcogen bonds between the imine nitrogen and selenium atom. The desired secondary amine-based dichalcogenides **33**–**39** were obtained by reducing the corresponding Schiff bases with $NaBH_4$ (Scheme 6).

Scheme 6. Synthesis of the *sec*-Amine-Based Dichalcogenides 33-39 by Using the Vilsmeier–Haack Formylation Method



The thiols/selenols **40**–**46** required for the deiodinase assays were obtained by treating the corresponding dichalcogenides (**33**–**39**) with $NaBH_4$. The ^{77}Se NMR spectra of compounds **41** and **42** showed that the signals for these compounds are significantly shifted upfield (δ = 109 and 110 ppm, respectively) relative to that for compound **2** (δ = 162 ppm), indicating that the amino group abstracts the proton from the selenol moiety. Similarly, the signal for one of the selenol groups in compounds **43**–**46** (δ = 76–85 ppm) was shifted upfield significantly relative to that for compound **3** (δ = 155 ppm). These observations suggest that the secondary amino group in compounds **40**–**46** can increase the nucleophilic reactivity by deprotonating the adjacent thiol or selenol moiety (Figure 5).

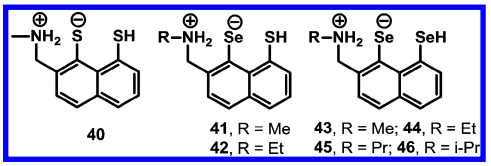


Figure 5. Deprotonation of thiol or selenol by an N-alkylamino group in compounds **40**–**46**.

Theoretical calculations also reveal that the amino group interacts with the adjacent thiol/selenol group in compounds **40**–**46** (Table S1, Supporting Information). Interestingly, the ^{77}Se NMR signal for one of the selenol groups in compounds **43**–**46** (δ = 76–85 ppm) was shifted upfield drastically relative to that of the other selenol in the same compounds (δ = 214–217 ppm). Furthermore, these signals were shifted ~60 ppm downfield relative to that of compound **3**, indicating that the deprotonation of one of the selenols in each compound by the amino group may decrease the nucleophilicity of the other selenol.

A comparison of the deiodinase activity of the amino-substituted compounds **40** and **43**–**46** to that of compounds **1** and **3** indicates that the introduction of an amino group significantly enhances the activity (Figure 6). The activity of

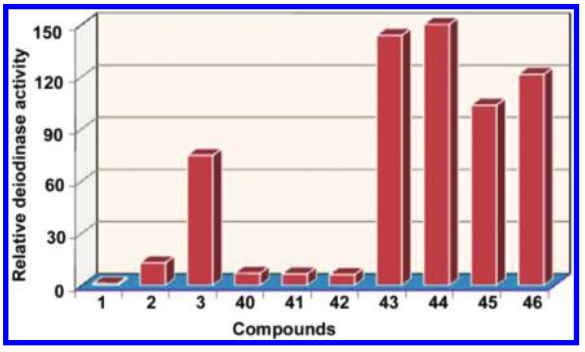


Figure 6. Comparison of the rate of deiodination of T4 by compounds **1**–**3** and **40**–**46**. The reactions were carried out in phosphate buffer (pH 7.5) at 37 °C. The final assay mixture contained 600 μM of **1**–**3** and **40**–**46**, 300 μM of T4, and 10 mM of DTT.

compound **40** was found to be almost 7-fold higher than that of compound **1**. Similarly, compounds **43**–**46** were found to be ~1.5–2-times more active than **3** under identical conditions. Unexpectedly, compounds **41** and **42**, having a thiol–selenol pair, were found to be ~2-times less active than compound **2**, indicating that the introduction of an N-methyl- or N-ethyl-amino group in close proximity of the selenol decreases the activity of the parent compound. This is probably due to the introduction of steric hindrance around the selenol, which decreases the possibility of an interaction between the selenol and T4. Therefore, in compounds **41** and **42**, the thiol group is expected to interact with iodine to form a halogen bond. In contrast, the selenol moiety in compound **2** interacts with

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iodine. When two thiols (compound **40**) or two selenols (compounds **43**–**46**) are present, the increase in the reactivity of one of the thiol or selenol groups may enhance the interactions between these compounds and T4. Although the activated selenol moiety is unlikely to participate in the halogen bonding directly due to steric hindrance, such activation should strengthen the chalcogen bonding, which in turn facilitates the cleavage of the C–I bond.

When the amino-substituted thiols/selenols **40**–**46** were employed for the deiodination instead of **3** (Scheme 5), the corresponding dichalcogenides **33**–**39** were obtained. The X-ray crystallographic and theoretical studies reveal that the secondary amino group in compounds **34**–**39** interacts noncovalently with the selenium to form chalcogen bonds (Figure 7 and Table 2).[39] The Se···N distances (2.591–2.623 Å) in these compounds are significantly shorter than the sum of the van der Waal's radii of nitrogen and selenium (3.45 Å). The interaction energies ($E_{Se\cdots N}$) obtained by NBO analysis also indicate that the nitrogen strongly interacts with the selenium atom upon formation of an intramolecular diselenide or selenenyl sulfide bond. Furthermore, the ^{77}Se NMR chemical shifts obtained experimentally for compounds **36**–**39** indicate that the signal for the selenium atom that interacts with nitrogen is shifted downfield (δ = 445–480 ppm) relative to that of the other selenium atom (δ = 341–350 ppm) in the same compound and that of the diselenide obtained from compound **10** (δ = 426 ppm). On the other hand, the signals for the selenium atoms that do not interact with nitrogen show significant upfield shift relative to that of **10**. These observations suggest that the nitrogen atom may start interacting with selenium along the course of a diselenide bond formation, which may facilitate the release of iodide from selenium during the deiodination (Scheme 5).

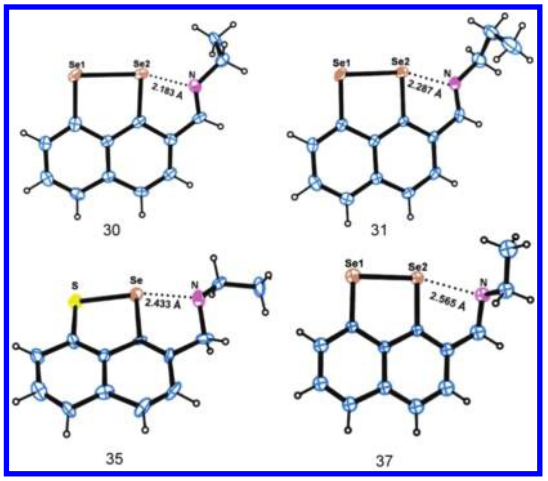


Figure 7. Single crystal X-ray structures of compounds **30**, **31**, **35**, and **37** showing strong Se···N interaction. The thermal ellipsoids were drawn at 50% probability.

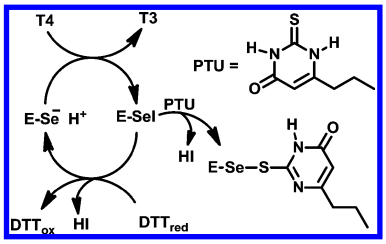
Table 2. Se···N Distances, ^{77}Se NMR Chemical Shifts, and Chalcogen Bond Energies Obtained for Compounds 34-39

compd	Se···N (Å)[a]	^{77}Se NMR[b] (Se1, Se2)	$E_{Se\cdots N}$ (kcal·mol^{-1})[a]
34	2.587	**577**	16.51
35	2.560	562	18.34
36	2.623	341, 480	14.94
37	2.594	344, 467	16.37
38	2.583	345, 470	16.94
39	2.591	350, 445	16.84

[a]The structures were optimized at the DFT level by using the B3LYP/6-31+G* basis set, and NBO analyses were performed at B3LYP/6-311+G** level of theory. [b]The NMR chemical shifts were obtained experimentally in $CDCl_3$ and are cited with respect to Me_2Se.

It has been shown that the antithyroid drug 6-*n*-propyl-2-thiouracil (PTU) inhibits ID-1 by reacting with the selenenyl iodide intermediate to form a stable selenenyl sulfide (Scheme 7).[1−3,40] Interestingly, PTU and related thiourea-based compounds do not inhibit the activity of ID-2 or ID-3. In experiments involving ID-3, no effect on deiodinase activity was observed up to 1 mM concentration of PTU at different DTT levels.[1−3,41] The mechanism shown in Scheme 5 suggests that the iodine is eliminated as iodide even before the formation of a well-defined selenenyl iodide intermediate, due to the formation of a chalcogen bond between the S/Se atoms at the *peri*-positions. As the formation of a stable Se–I bond is required for the formation of a selenenyl sulfide,[42] PTU does not inhibit the activity of ID-3. In agreement with this, no inhibition of activity was observed when the deiodination of T4 was carried out with compound **3** in the presence of PTU up to 0.45 mM concentration (Figure S44 of the Supporting Information). In contrast to thiols such as DTT or glutathione that can form intermolecular selenenyl sulfides upon reaction with diselenides, PTU is inactive toward diselenides.

Scheme 7. Inhibition of ID-1 by the Thiourea-Based Antithyroid Drug, *n*-Propyl-2-thiouracil (PTU)



While thiourea drugs such as PTU react with the selenenyl iodide intermediate of ID-1 to form a selenenyl sulfide as a dead-end product (Scheme 7), the other known inhibitors of ID-1, such as gold thioglucose (GTG) and iodoacetic acid (IAA), may react with the selenol group of the enzyme. In contrast, ID-2 and ID-3 are not inhibited by GTG and IAA.[1,2] Although IAA irreversibly inhibits the activity of several Cys peptidases,[43] the Sec-containing glutathione peroxidase (GPx),[44] and thioredoxin reductase (TrxR)[45] by forming the corresponding alkylated Cys or Sec derivatives, the reason for the insensitivity of ID-3 toward IAA is not clear. When compound **3** was treated with IAA, the reaction did not produce the expected Se-carboxymethylated derivative (**47**) but instead produced diselenide **6** with the elimination of acetic acid. The formation of acetic acid in this reaction indicates that IAA is rapidly deiodinated by compound **3**. Similarly, iodoacetamide, bromoacetic acid, and bromoacetamide were dehalogenated by **3**, although the debromination was found to be much slower than the deiodination. The mechanism of dehalogenation may involve a cooperative chalcogen and halogen bonding as shown in Scheme 5. As bromine is a weaker halogen bond donor than iodine, the debromination is slower than the deiodination. In contrast to the reactivity of compound **3**, compound **10**, which lacks the second selenol

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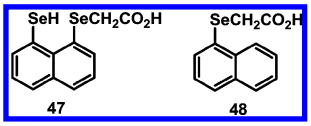
moiety, underwent facile carboxymethylation by IAA to produce compound **48** as the major product. These observations suggest that IAA may undergo rapid deiodination in the presence of ID-3, which may account for the insensitivity of this enzyme toward IAA.



CONCLUSIONS

In this paper, the deiodinase activity of a series of *peri*-substituted naphthalenes has been described. These compounds remove iodine selectively from the inner-ring of thyroxine (T4) and 3,5,3′-triiodothyronine (T3) to 3,3′,5′-triiodothyronine (rT3) and 3,3′-diiodothyronine (3,3′-T2), respectively. The naphthyl-based compounds having two selenol groups in the *peri*-positions are remarkably more active than ones having two thiol groups or a thiol-selenol pair. The cooperative effects of nucleophilic thiol and selenol groups play an important role in the inner-ring deiodination of T4 and T3. Experimental and theoretical investigations reveal that the interaction between the iodine and chalcogen (S or Se) (halogen bond) and the *peri*-interaction between two chalcogen atoms (chalcogen bond) are important for the deiodinase activity. Although the formation of a halogen bond leads to elongation of the C−I bond, a complete cleavage of the C−I bond occurs when the two chalcogen atoms in the *peri*-positions interact with each other to facilitate the transfer of more electron density to the C−I σ^* orbitals. The higher activity of amino-substituted selenium compounds can be ascribed to the deprotonation of the thiol/selenol moiety by the amino group, which not only increases the strength of the halogen bond but also facilitates the chalcogen−chalcogen interactions. This study also suggests that the formation of a chalcogen bond between the S/Se atoms at the *peri*-positions facilitates the release of iodide from the substrate. As the formation of a stable Se−I bond is required for the formation of a selenenyl sulfide, the ID-1 inhibitor PTU does not inhibit the activity of ID-3. The insensitivity of ID-3 toward iodoacetic acid (IAA) can be ascribed to the facile deiodination of IAA by the enzyme.

ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, and ^{77}Se NMR spectra for all the new sulfur/selenium compounds, HPLC traces obtained for the deiodination of T4 by **2** and **3**, effect of PTU on the deiodination of T4 by **3**, archive entries for the optimized geometries, NBO charges, and the full reference of ref 15. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(31) This compound is used as a theoretical model for this study. Attempts to synthesize the selenenyl iodide by treating the corresponding diselenide with iodine were unsuccessful, as there is no substituent in the compound that can stabilize the Se−I bond (see ref 36).
(32) The chalcogen bond is considered as a sister noncovalent bond to the halogen bond: Wang, W.; Ji, B.; Zhang, Y. *J. Phys. Chem. A* **2009**, *113*, 8132−8135.
(33) In naphthalene derivatives, the proximity effects of two substituents in the 1,8-positions are considered as *peri*-interactions. A conformational rigidity is imposed when two atoms or groups are introduced to these positions. Recently, noncovalent interactions involving two chalcogen atoms in the naphthalene *peri*-positions have been reported: (a) Nakanishi, W.; Hayashi, S.; Toyota, S. *J. Org. Chem.* **1998**, *63*, 8790−8800. (b) Nakanishi, W.; Hayashi, S.; Toyota, S. *Chem. Commun.* **1996**, 371−372. (c) Nakanishi, W.; Hayashi, S. *J. Phys. Chem. A* **1999**, *103*, 6074−6081. (d) Hayashi, S.; Nakanishi, W. *J. Org. Chem.* **1999**, *64*, 6688−6696. (e) Kilian, P.; Knight, F. R.; Woollins, J. D. *Chem.—Eur. J.* **2011**, *17*, 2302−2328 and references therein.
(34) The selenenyl iodides corresponding to compounds **11** and **12** were synthesized by treating the respective diselenides with iodine. The ^{77}Se NMR spectra indicate that the selenenyl iodides are stabilized by Se···N and Se···O noncovalent interactions (Figures S42 and S43, Supporting Information).
(35) As the selenol moiety in selenocysteine residues exists predominantly in its selenolate form at physiological pH, activation by a His residue is probably not very important. Therefore, the deprotonation of Cys by a His residue at the active site of ID-1 to form a thiolate−imidazolium ion pair cannot be ruled out. In such a case, the reactivity of a Sec−Cys pair is probably similar to or even better than that of two Sec residues. By using ^{77}Se NMR spectroscopy, Mobli *et al.* showed that the deprotonation of a Sec residue in peptides can take place at pH as low as 3 and that Sec residues in different environments can exist completely in their selenolate forms at pH above 6.0: Mobli, M.; Morgenstern, D.; King, G. F.; Alewood, P. F.; Muttenthaler, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11952−11955.
(36) The selenium centers in selenenyl iodides can readily accept electrons from donor atoms such as nitrogen, leading to elongation of the Se−I bond. In some cases, such interactions can lead to elimination of iodide. For different types of selenium−iodine contacts, see: du Mont, W.-W.; Martens-von Salzen, A.; Ruthe, F.; Seppälä, E.; Mugesh, G.; Devillanova, F. A.; Lippolis, V.; Kuhn, N. *J. Organomet. Chem.* **2001**, *623*, 14−28.
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